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Is the Venner-PneuX endotracheal tube system a cost-effective option for post cardiac surgery care?

Running head: Economic evaluation of the PneuX system.

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Keywords: economic evaluation, endotracheal tubes, ventilator-associated pneumonia, cost-effectiveness analysis, cost-utility analysis

Abstract

Background: Ventilator-associated pneumonia (VAP) is common and costly. In a recent randomized controlled trial, the Venner-PneuX (VPX) endotracheal tube system was found to be superior to standard endotracheal tubes (SET) in preventing VAP. However, VPX is considerably more expensive. We evaluated the costs and benefits of VPX to determine whether replacing SET with VPX is a cost-effective option for intensive care units.

Methods: We developed a decision analytic model to compare intubation with VPX or SET for patients requiring mechanical ventilation post cardiac surgery. The model was populated with existing evidence on costs, effectiveness and quality of life. Cost-effectiveness and cost-utility analyses were conducted from an NHS hospital perspective. Uncertainty was assessed through deterministic and probabilistic sensitivity analyses.

Results: Compared to SET, VPX is associated with an expected cost saving of £738 per patient. VPX led to a small increase in quality-adjusted life years (QALYs), indicating that the device is overall less costly and more effective than SET. The probability of VPX being cost-effective at £30,000 per QALY is 97%. VPX would cease to be cost-effective if (i) it led to a risk reduction smaller than 0.02 compared to SET, (ii) the acquisition cost of VPX was as high as £890 or, (iii) the cost of treating a case of VAP was lower than £1,450.

Conclusions: VPX resulted in improved outcomes and savings which far offset the cost of the device, suggesting that replacing SET with VPX is overall beneficial. Findings were robust to extreme values of key parameters.

Introduction

Between 8% and 28% of all patients receiving mechanical ventilation develop ventilator-associated pneumonia (VAP), a common infection caused by pathogens colonizing a patient's upper aero-digestive tract (1). VAP is linked to higher mortality, with critically ill patients who develop VAP being twice as likely to die (2), and substantial use of health care resources, chiefly due to prolonged stay and additional diagnostic and therapeutic interventions (3-5). Existing studies report the additional health care cost attributed to VAP to be between $10,000 (£7,520) and $60,000 (£45,110) per case (2, 4, 6).

VAP is caused by contaminated aero-digestive secretions pooling in the subglottic space above the inflated cuff of an endotracheal tube (ET). The cuff aims to provide an airtight seal to facilitate maintenance of positive end expiratory pressure; however, micro-folds developing in the inflated cuff allow the contaminated subglottic secretions to micro-aspirate past the cuff into the lower respiratory tract (7, 8). Given this, there has been considerable interest in ETs that retain adequate cuff pressure against the tracheal wall (9).

The significant health and economic burden of VAP has led to increasing interest in the development and use of interventions aimed at preventing its occurrence (10, 11). Venner-PneuX (VPX) is an endotracheal system that aims to monitor, control and maintain a safe inflation volume and pressure (30cm H_2O) within the cuff in order to reduce the risk of tracheal injury.

In a recent randomized controlled trial funded by the Department of Health in the UK (ISRCTN 45757289), VPX was associated with a significant reduction of VAP as compared to a standard, widely used endotracheal tube (SET) (odds ratio 0.45, P = 0.03) (12).

However, in an environment of constrained resources, a rigorous economic assessment of VPX is necessary prior to introducing the device in the intensive care setting. As VPX costs considerably more than standard tubes (an additional £145 per tube), providers of critical care services need to know whether, and to what extent, the effectiveness of VPX in preventing VAP compensates for the higher acquisition cost of the device. The need for an economic analysis has been highlighted by the National

Institute for Health and Care Excellence (NICE) in the UK in a recent report, which highlights the potential of VPX to reduce intensive care unit (ICU) and hospital stay but stresses the lack of evidence on its cost-effectiveness (13).

We undertook an economic evaluation to determine the additional costs (device acquisition cost, overall treatment cost) and benefits (number of VAP cases prevented, quality-adjusted life years (QALYs) gained) associated with VPX in comparison to SET for patients requiring mechanical ventilation in a critical care setting.

Materials and Methods

We built a decision model to evaluate the expected costs and benefits associated with VPX and SET. The evaluation was carried out from the perspective of NHS secondary health care service providers. The target population comprised hospitalised patients who required intubation after major cardiac surgery. Given the acute nature of VAP and the focus on secondary care providers, the time horizon was set at 28 days after surgery. Monetary values were expressed in 2016 UK sterling (£1=$1.33) (14).

Model structure

The expected costs and consequences of VPX and SET were assessed through a simple decision tree, the graphical representation of which can be seen in Figure 1. Paths (branches) in the model represent eventualities following the choice of endotracheal tube for a patient who has undergone cardiac surgery and requires post-operative mechanical ventilation. Analyses were carried out in STATA (StataCorp, Release 12. College Station, TX, US) and Microsoft Excel (Microsoft, Version 2010, Redmont, WA, US).

Model inputs

Inputs used in the model are detailed in Supplemental Material 1. Key information on the effectiveness of VPX in preventing VAP was obtained from a clinical trial comparing VPX against SET (ISRCTN 45757289). A detailed description of the trial and its findings is given in Gopal et al. (12). Briefly, the

trial randomized 240 consenting patients scheduled to undergo cardiac surgery to either SET (n=120) or VPX (n=120) and found a lower incidence of VAP in the VPX group compared to SET (10.8% vs. 21%, odds ratio: 0.45, p=0.03), although there was no statistically significant difference in ICU stay and in-hospital mortality. The obtained data were used to establish the risk of developing VAP associated with the use of each tube, the absolute risk difference between VPX and SET and the probability that a patient will contract VAP with each of the compared options ($P(VAP)_{VPX}$ and $P(VAP)_{SET}$, respectively).

Costs associated with each treatment were estimated according to the acquisition cost of VPX and SET and the estimated cost of care provided to patients with and without VAP. The acquisition cost of VPX (AqC_{vpx} in the model) was obtained from the UK distributor of the device (Qualitech Healthcare Limited, Maidenhead, UK). The mean costs associated with treatment of patients who did and did not develop VAP (C_{VAP} and C_{noVAP}, respectively) were obtained from a published propensity-matched study of prospectively collected resource use data drawn from the same hospital as the study that provided estimates of the effectiveness of VPX and SET (12). Details of this study can be found in Luckraz et al. (15). In brief, all patients undergoing cardiac surgery at the Heart & Lung Centre, New Cross Hospital during the period of April 2011 to December 2014 were initially selected (n=3416). Patients who were diagnosed to have developed definite VAP using the CDC definition (16) and the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) clinical criteria (17) were included in the VAP group (n=338) and were matched to patients who did not develop VAP using propensity scores generated from a logistic regression model. Ethical approval for this study was provided by the Ethical Committee West of Scotland Research Ethic Service (reference: 15/WS/0142) in July 2015. Anonymised information on each patient's inpatient stay and use of health care resources was extracted from routinely collected Healthcare Resource Group (HRG) codes available from the hospital's records. HRG codes are standard clinical groupings which detail the amount and composition of health care resources that a patient with a particular condition or diagnosis is expected to use (18). Given the short time horizon of this analysis, neither costs nor benefits were discounted.

The analysis was extended to assess the effect of VPX and SET in terms of QALYs, a measure that combines time spent in a particular health state with estimates of the preference-based health related quality of life (utility) associated with the state. QALYs associated with and without contraction of VAP ($QALY_{VAP}$ *and* $QALY_{noVAP}$, respectively) were calculated over 28 days as the sum of two components: the product of time and utility associated with stay in the ICU, and the product of time and utility for stay in ward:

$$QALY_i = U_{ICU} \times T_{i,ICU} + U_{Ward} \times T_{i,Ward}$$

where i represents the existence or absence of VAP (i=VAP, noVAP), U represents the utility associated with stay in ICU or ward, and T represents the average time (in days) that patients are expected to spend in ICU and ward. Estimates for the time spent in ICU and ward for patients with and without VAP were obtained from anonymised patient-level data collected in the same matched cohort study that contributed data on resource use. As in Edwards et al. (19), it was assumed that an intubated patient in critical care would experience a level of quality of life comparable to being unconscious. A quality of life value for a patient recovering in ward was taken from Eddleston et al. (20). Alternative values were used in sensitivity analyses.

Cost-effectiveness and cost-utility analyses

Cost-effectiveness and cost-utility analyses were conducted to compare VPX against SET through the developed model. Results were obtained by carrying out standard roll-back calculations (21). The total cost for each option (i.e. VPX or SET) comprises the acquisition cost of the technology plus the expected cost associated with each possible eventuality (i.e. developing or not developing VAP). The latter is calculated as the cost of the event of interest (VAP) weighted by the probability of the event occurring under each option ($P(VAP)_{VPX}$ and $P(VAP)_{SET}$ for VPX and SET, respectively).

Findings from the cost-effectiveness analysis are expressed as i) cost per case of VAP avoided and ii) total net benefit. The cost per case of VAP avoided represents the additional intubation-related expenditures for avoiding a case of VAP. The total net benefit extends these findings by accounting for

the monetary value of avoiding a case of VAP. This metric reflects the difference between the overall costs of VPX and SET, when these costs include the outlay for treating a case of VAP.

$$TNB_{(SET\ vs\ VPX)} = (AqC_{SET} + TotCost_{SET}) - (AqC_{VPX} + TotCost_{VPX})$$

where AqC_{SET} and AqC_{VPX} stand for the acquisition cost of SET and VPX respectively, and $TotCost_{SET}$ and $TotCost_{VPX}$ represent the expected cost of VAP for patients intubated with SET and VPX respectively, given the probability of contracting VAP associated with each tube.

Results of the cost-utility analysis reflect the additional cost (or cost saving) associated with a gain of an additional QALY. Findings are given as point-estimate values and are plotted in cost-effectiveness acceptability curves (CEACs) (22, 23). CEACs show the probability of VPX being cost-effective across a range of possible monetary values representing decision makers (or society's) the willingness to pay to for a unit of outcome—here, a case of VAP avoided and an additional QALY.

Sensitivity analysis

In line with recommendations (24, 25), uncertainty in the model was assessed through probabilistic and deterministic sensitivity analyses. The former involved assigning probability distributions to key parameters and carrying out a large number of Monte Carlo simulations (26). In each of these simulations, values were drawn at random from the specified distributions of uncertain parameters. Each set of drawn values was entered in the model and results were re-calculated to give 5,000 estimates of the costs and effects associated with each treatment (27). Parameters assigned probability distributions included the probability of a patient developing VAP when intubated with VPX and SET, the quality of life in ICU and ward and the cost associated with patients who did and did not develop VAP.

In addition to probabilistic sensitivity analysis, deterministic analyses were carried out to assess the robustness of the results to alternative values of key parameters. Threshold analysis was also undertaken to determine the values of these parameters (i.e. the effectiveness of VPX and SET, the acquisition cost

of VPX and SET and the additional cost of VAP) above and below which conclusions about the cost-effectiveness of the compared options change.

Results

Base case cost-effectiveness and cost-utility results

The additional VPX acquisition cost per VAP case avoided is £1,450. This value reflects the extra cost of intubating 10 patients with VPX as opposed to SET in order to prevent one case of VAP. Preventing a case of VAP is associated with a saving of £8,829, thus, subtracting this value from the additional cost of VPX, one can obtain an estimate of the total net benefit associated with VPX. A hospital would need to invest £1,450 in order to offer VPX to 10 patients, but this investment would result in an additional case of VAP avoided, which would save £8,829. This results in a total net benefit of £7,379 for 10 patients, or £738 per patient (Table 1).

In the cost-utility analysis, VPX was associated with cost savings due to avoided VAP and a greater number of QALYs due to reduced stay in ICU, suggesting that the device dominates SET (i.e. is less costly and more effective than SET). As VPX is a dominant option, calculating an ICER for the particular comparison is not necessary (21).

Sensitivity analysis results

Uncertainty around the results was explored through probabilistic, deterministic and threshold sensitivity analyses.

Results of deterministic sensitivity analyses showed that, for all alternative values of uncertain parameters, VPX was overall less costly and resulted in greater numbers of QALYs. The total net benefit for different values and assumptions ranged from £421 to £2,390 (see Supplemental Material 2).

The outputs of probabilistic sensitivity analysis for the cost-effectiveness and the cost-utility analyses are depicted in cost-effectiveness planes (Figures 2 and 3) and are plotted in CEACs (Figure 4). The

probability of VPX being cost-effective at a range of possible values of a provider's willingness to pay to avoid a case of VAP is 18% at £1,000, it increases to 72% at £2,000 and it reaches 97% at £10,000. In terms of cost per QALY, the probability of VPX being cost-effective is 96% at willingness to pay values between £0 and £30,000 per QALY and it rises slowly to 97% for values over £80,000 per QALY (not shown here).

Threshold analysis sought to explore the cut-off values above and below which VPX would cease to be cost-effective. Detailed results can be found in Supplemental Material 3. Assuming that there is no difference in the rate of VAP for VPX and SET, the adoption of VPX would result in a net cost of £145 per patient, equal to the additional acquisition cost of VPX. For any absolute risk reduction values over 0.02, the cost savings would exceed the additional cost of VPX and result in net benefit. Holding the absolute risk reduction at its base case value, if the additional cost of VAP was as low as £2,000, VPX would still be associated with a total net benefit of about £55 per patient. If this cost was £20,000, the total net benefit would exceed £1,800 per eligible patient. Lastly, if the device's acquisition cost was three times less than its current price (i.e. £50, as opposed to £150, the total net benefit per patient would be approximately £840). Conversely, a cost of VPX three times as high would result in a total net benefit of about £440. VPX would cease to result in a net benefit if its acquisition cost was greater than £890.

Comment

Tackling health care-associated infections, including VAP, is an important policy objective for health systems around the world (28-30). Different prevention measures are available, but it is important to ensure that replacing standard care with a particular technology represents an efficient use of scarce resources.

Our analysis shows that the additional cost of adopting VPX is £1,450 per case of VAP avoided. This cost is well below the savings resulting from avoiding the need to treat a case of VAP. The total net benefit, that is, the cost savings associated with VPX minus the additional acquisition cost of VPX, is £738 per eligible patient. VPX would still lead to cost savings which would cover its acquisition cost even if (i) the acquisition cost of VPX was as high as £890 (about 6 times as high as the reference

acquisition cost), (ii) the absolute risk reduction associated with VPX over SET is not less than 0.02, or (iii) the savings from preventing a case of VAP were as low as £1,450, far below the observed values used in this analysis or other values cited in the literature (2, 5, 6, 31).

Our work presents certain strengths. We developed a simple, parsimonious model which can be easily updated should newer data emerge in the future. The model was populated with available with effectiveness estimates from a randomized controlled trial of VPX, while costs were calculated on the basis of patient-level data from a matched cohort in the same UK hospital, using actual HRG tariffs. In the UK, HRG codes are recorded for each patient and the resulting patient-level data is used to calculate payments to National Health Service providers (32). Uncertainty was explored via probabilistic and deterministic sensitivity analyses, and threshold analysis was carried out to evaluate the possible impact of different scenarios on the results (24).

Despite this, findings are subject to certain uncertainties. First, the fact that evidence comes from a single randomized trial, the LoVAP study, adds a layer of uncertainty. To the authors' best knowledge, this trial is the only source of estimates of the effectiveness of VPX as compared to SET which are relevant to the question we set out to answer. This study involved 120 patients per arm, on the basis of a standard sample size calculations for the primary outcome of VAP occurrence. Should further rigorous data on the effectiveness of VPX and SET in preventing VAP become available in the future, this can be incorporated in our model. Secondly, there is a lack of robust estimates of the health-related quality of life associated with patients in critical care settings, largely due to practical and ethical difficulties in collecting patient-reported data (33). In line with existing studies, we assumed that quality of life will be higher (i.e. better) when a patient is recovering in ward than when she/he is intubated in ICU. Thus, the total QALYs associated with VPX and SET are largely driven by the amount of time spent in ICU or ward and are directly related to each option's effectiveness in preventing VAP and further stay in ICU. This also applies to costs: estimates of the cost of developing and not developing VAP obtained from a matched study were applicable to both VPX and SET, with the total cost, as expected, depending on the likelihood of a patient developing VAP with either VAP or SET intubation. Drawing on some of the authors' experience with VPX, we would recommended that, unless clinically indicated, the

endotracheal tube (ETT) used at the time of intubation (initial anesthesia) for cardiac surgery should not be changed to another ETT, as this change of ETT in itself can predispose to VAP. Hence for the benefit of VPX to be gained, it is preferable that the device is used from the time of the initial intubation.

To the authors' best knowledge, this is the first economic evaluation of the Venner PneuX endotracheal tube against a standard tube. In a recent study, Branch-Elliman and colleagues (34) evaluated the cost-effectiveness of different VAP preventing strategies. Lack of data from a head-to-head comparison of the evaluated treatments meant that the authors had to combine information from different sources. The authors found subglottic endotracheal tubes to be cost-effective at a willingness-to-pay threshold of $50,000 to $100,000 (£37,590 to £75,190). Although this analysis provides useful insights, the authors acknowledge that key inputs were drawn from a study published almost 15 years ago, in 2002. Our study addresses this issue by using evidence of the cost of treating patients with and without VAP from the same study.

Conclusions

Overall, findings suggest that the benefits of VPX exceed its additional cost, resulting in a total net benefit of £738 per patient. VPX resulted in lower costs and a gain in QALYs. The results are robust to extreme values of the key parameters in the analysis.

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Table 1. Results of cost-effectiveness and cost-utility analyses

Summary table	Total Cost	Total QALYs	Cost per case avoided (VPX vs SET)	Total Net Benefit (per patient, VPX vs SET)	ICER (VPX vs SET)
VPX	£7,401	0.025	£1,450	£738	Cost savings and QALYs gained
SET	£8,139	0.024			

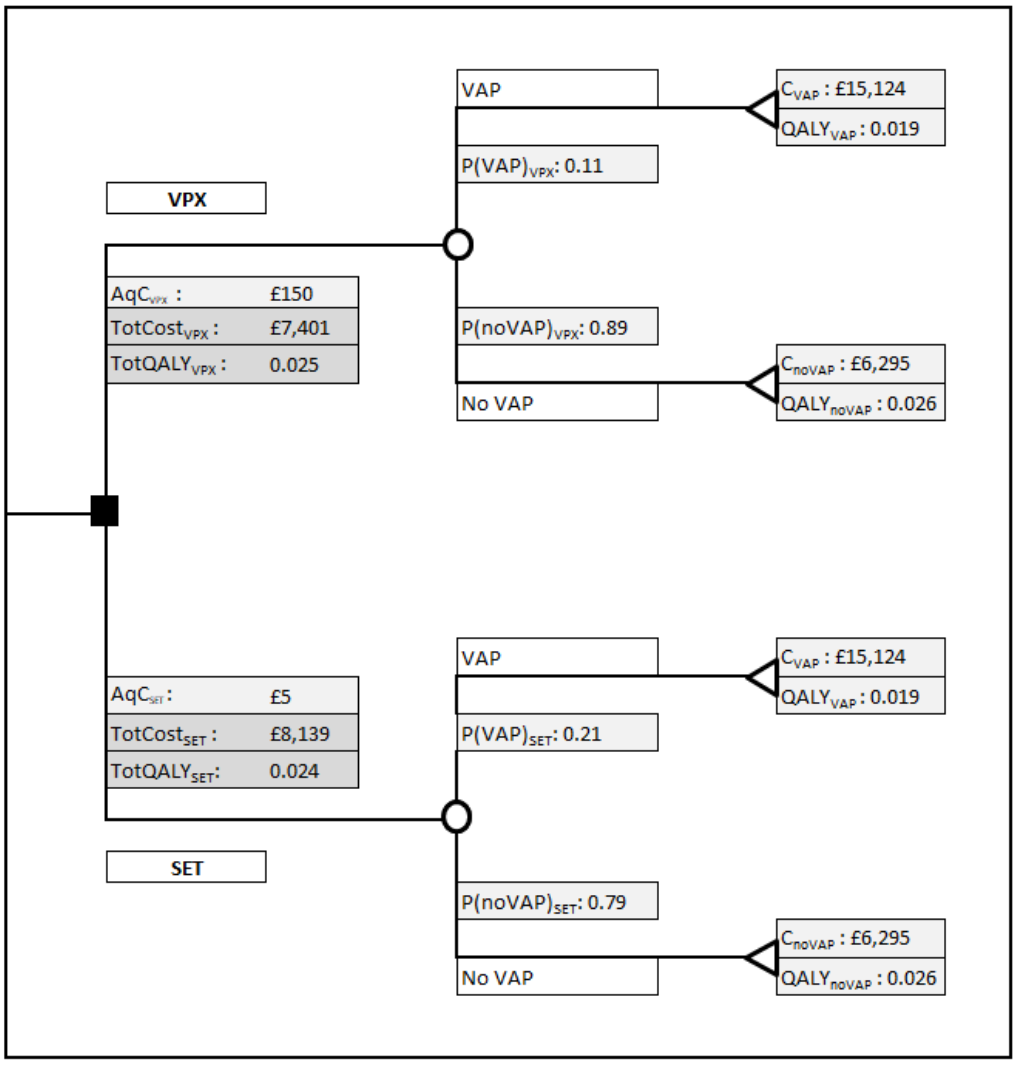
Figure legends

Figure 1. Structure of the decision model.

Figure 2. Cost-effectiveness plane showing 5000 paired estimates of the difference in cost and difference in number of cases of VAP avoided (VPX vs SET)

Figure 3. Cost-effectiveness plane showing 5000 paired estimates of the difference in cost and difference in QALYs (VPX vs SET)

Figure 4. Cost-effectiveness acceptability curves showing the probability of VPX being cost-effective.



AqC_{VPX}: acquisition cost of VPX; **$TotCost_{VPX}$**: total expected cost with VPX; **$TotQALY_{VPX}$**: total expected QALYs associated with VPX; AqC_{SET}: acquisition cost of SET; **$TotCost_{SET}$**: total expected cost with SET; **$TotQALY_{SET}$**: total expected QALY associated with SET; **$P(VAP)_{VPX}$**: probability of developing VAP with VPX; **$P(noVAP)_{VPX}$**: probability of not developing VAP with VPX; **$P(VAP)_{SET}$**: probability of developing VAP with SET; **$P(noVAP)_{SET}$**: probability of not developing VAP with SET; **C_{VAP}**: cost of treating a patient who developed VAP; **$QALY_{VAP}$**: QALYs associated with a patient who developed VAP; **C_{noVAP}**: cost of treating a patient who did not develop VAP; **$QALY_{noVAP}$**: QALYs associated with a patient who did not develop VAP.

Model input parameters are given in lightly shaded boxes; results calculated within the model appear in dark shaded boxes.

Figure 1. Structure of the decision model.

Supplemental Material 1. Model inputs and associated probability distributions.

Parameter	Point estimate value	Probability distribution	Source/comment
Costs			
VPX acquisition cost (AqC_{VPX})	£150	Gamma (100, 1.5)	Value taken from distributor and NICE (13). Distribution fitted assuming a standard deviation of 1/10 of the acquisition cost value.
Standard endotracheal tube (Portex tracheal tube) acquisition cost (AqC_{SET})	£5	Gamma (100, 0.05)	Value taken from the procurement department of the Royal Wolverhampton NHS Trust. Distribution fitted assuming a standard deviation of 1/10 of the acquisition cost value.
Mean NHS treatment cost for a patient who developed VAP post cardiac surgery (C_{VAP})	£15,124	Gamma (0.86, 7317)	Values obtained from propensity matched cohorts who did and did not develop VAP at the Royal Wolverhampton NHS Trust. Distribution fitted to observed mean and standard deviation values.
Mean NHS treatment cost for a patient who did not developed VAP post cardiac surgery (C_{noVAP})	£6,295	Gamma (0.634, 23852)	
Effectiveness and quality of life			
Probability of developing VAP while intubated with VPX ($P(VAP)_{VPX}$	0.11	Beta (13, 107)	Point estimates obtained from Gopal et al. (12). Distribution fitted to reported values.
Probability of developing VAP while intubated with SET ($P(VAP)_{SET}$	0.21	Beta (25, 95)	
Preference-based quality of life (utility) while intubated in ICU	-0.402	Gamma (7.18 0.056)	Point estimate values calculated on the basis of relevant literature (18, 19). Distribution fitted to reported values.
Preference-based quality of life (utility) while recovering on ward	0.726	Gamma (132.45, 0.013)	

VPX: Venner-PneuX; VAP: ventilator-associated pneumonia; SET: standard endotracheal tube; ICU: intensive care unit.

Supplemental Material 1. Results of deterministic sensitivity analyses

Alternative values	Parameter	Total Net Benefit (VPX vs SET)	Difference in Costs	Difference in QALYs	Cost per QALY	Source/comment
Additional cost of VAP	£5,660	£421	£421	0.0007	VPX less costly and more effective.	Published literature (2)
	£7,220	£577	£577	0.0007	VPX less costly and more effective	Published literature (4)
	£17,261	£1,581	£1,581	0.0007	VPX less costly and more effective	Published literature (31)
	£25,351	£2,390	£2,390	0.0007	VPX less costly and more effective	Published literature (6)
Quality of life in ICU and ward	ICU: 0.3 Ward: 0.5	£738	£738	0.0001	VPX less costly and more effective	Published literature (35)
	ICU: -0.166 Ward: 0.516	£738	£738	0.0004	VPX less costly and more effective	Based on the EQ-5D valuation of a health state with the following attributes: In ICU: Mobility: I am confined to bed; Self-care: I'm unable to wash or dress myself; Usual activities: I am unable to perform my usual activities; Pain/discomfort: I have moderate pain or discomfort; Anxiety/Depression: I am moderately anxious/depressed).

						In ward: Mobility: I have some problems in walking about; Self-care: I have some problems washing or dressing myself; Usual activities: I have some problems with performing my usual activities; Pain/discomfort: I have moderate pain or discomfort; Anxiety/Depression: I am moderately anxious/depressed).

Supplementary Material 3

Table 1. Total net benefit for different values of absolute risk reduction of VAP

Table 2. Total net benefit for different values of the additional cost of treating VAP

Table 3. Total net benefit for different values of the acquisition cost of VPX

SDC Table 1. Total net benefit for different values of absolute risk reduction of VAP

Absolute Risk Reduction (VPX vs SET)	Total Net Benefit
0.00	-£145*
0.02	£0
0.04	£208
0.06	£385
0.08	£561
0.1 (base case value)	£738
0.12	£914
0.14	£1,091
0.16	£1,268
0.18	£1,444
0.2	£1,621
* Negative values indicate that VPX is overall more costly than SET	

SDC Table 2. Total net benefit for different values of the additional cost of treating VAP

Additional Cost of VAP	Total Net Benefit
£1450	£0
£2000	£55
£4000	£255
£6000	£455
£8000	£655
£8829 (base case value)	£738
£10,000	£855
£12,000	£1055
£14,000	£1255
£16,000	£1455
£18,000	£1655
£20,000	£1855

SDC Table 1. Total net benefit for different values of the acquisition cost of VPX

Acquisition cost of VPX	Total Net Benefit
£50	£838
£150 (base case value)	£738
£250	£638
£350	£538
£450	£438
£550	£338
£650	£238
£750	£138
£850	£38
£888	£0